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First Named Inventor	Kim, Raymond
Art Unit	1645
Examiner Name	Jana A. Hines
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ENCLOSURES *(Check all that apply)*

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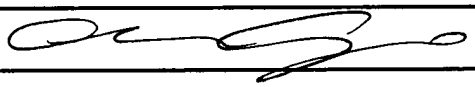
Signature			
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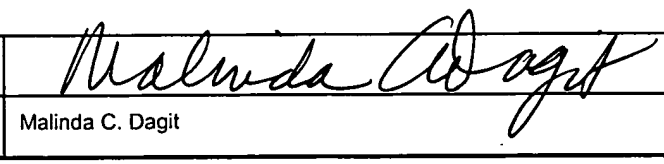
Signature			
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TOWNSEND and TOWNSEND and CREW LLP

By: Malvida Adogit

PATENT
Atty. Docket No.: 020144-003100US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 6593
Raymond Kim	Examiner: Jana A. Hines
Application No.: 10/650,261	Technology Center/Art Unit: 1645
Filed: August 27, 2003	
For: FILM LAYER FOR DETECTION OF IMMOBILIZED ANALYTES	APPELLANT'S BRIEF UNDER 37 C.F.R. §41.37
Customer No.: 20350	

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Sir:

In response to the Notification of Non-Compliant Appeal Brief mailed January 28, 2008, Appellant hereby resubmits this appeal brief to replace the previous versions.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest in U.S. Application No. 10/650,261 is Zyomyx, Inc.

II. RELATED APPEALS AND INTERFERENCES

There are no other pending appeals by Appellant or interferences in which Appellant is involved the outcome of which would directly affect the decision by the Board of Patent Appeals and Interferences in this pending appeal.

III. STATUS OF THE CLAIMS

Claims 1-26 were originally filed. Subsequently, claims 1-13 and 26 were canceled. Claims 14-25 are pending in this application. In the final Office Action mailed June 20, 2006, the Examiner rejects claims 14-22 and 25 under 35 U.S.C. §102(b), alleging anticipation by U.S. Patent No. 4,806,312 (Greenquist *et al.*). The Examiner also rejects claims 23 and 24 under 35 U.S.C. §103(a), alleging obviousness over the '312 patent in view of U.S. Patent No. 5,436,161 (Bergstrom *et al.*). The rejections of claims 14-25 are being appealed.

IV. STATUS OF THE AMENDMENTS

No amendment was filed subsequent to the final Office Action of June 20, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter in this appeal relates to an apparatus for detecting the specific binding between an analyte and its ligand. This apparatus includes at least two layers: the first is the analyte layer, which comprises an analyte that has a ligand-binding site and is immobilized to a solid support. The second layer is the film layer, which comprises a ligand in a ligand zone. When the ligand zone is wet, the ligand

can diffusibly migrate to bind the analyte via the anylyate's ligand-binding site and form a detectable product.

Claim 14

The subject matter claimed in independent claim 14 is an apparatus comprising a molecular analyte layer and a film layer. The analyte layer comprises a molecular analyte immobilized onto a solid support, and the analyte has a molecular ligand binding site. The film layer comprises a molecular ligand zone in which there is a molecular ligand. Upon wetting of the ligand zone, the ligand can diffusibly migrate to the ligand binding site of the analyte to produce a detectable product.

Support for this claim can be found in the specification, *e.g.*, on page 3, lines 21-27, and in original claim 14.

Claim 24

The subject matter claimed in dependent claim 24 is the apparatus of claim 14, further defined in that the molecular ligand zone comprises a molecular ligand within a hydrogel, which comprises acrylamide or agarose.

Support for this claim can be found in the specification, *e.g.*, on page 10, line 8, to page 11, line 6, page 12, lines 3-13, and in original claims 23 and 24.

VI. GROUNDS OF REJECTION TO BE REVIEWED AND APPEALED

1. The rejection of claims 14-22 and 25 for alleged anticipation by Greenquist.

2. The rejection of claims 23 and 24 for alleged obviousness over Greenquist in view of Bergstrom.

VII. ARGUMENT

A. The Rejection for Anticipation Is Improper

Claims 14-22 and 25 stand rejected under 35 U.S.C. §102(b) because the Examiner alleges that the claimed invention is anticipated by Greenquist. Appellant respectfully traverses this rejection and argues that the rejection is improper, because Greenquist does not teach or suggest at least one limitation of the pending claims: an analyte that is immobilized in one layer and specifically binds a ligand to form a detectable product.

1. Standard for Establishing Anticipation

To anticipate a pending claim, a prior art reference must provide, either expressly or inherently, each and every limitation of the pending claim. MPEP§2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

2. Greenquist Does Not Provide All Claim Limitations

In the Final Office Action of June 20, 2006, claims 14-22 and 25 are rejected under 35 U.S.C. §102(b) for alleged anticipation by Greenquist *et al.* (U.S. Patent No. 4,806,312). Appellant contends that the rejection is clearly in error, because the cited reference does not expressly provide all limitations of the pending claims, *e.g.*, an analyte that is immobilized in one layer and specifically binds a ligand to form a detectable product.

The pending claims of this application are drawn to a multiple-layer detection apparatus for detecting the specific binding between an analyte and its ligand. The apparatus has at least two layers: an analyte layer and a ligand layer. The analyte layer contains one immobilized analyte that has a binding site for its ligand. The ligand layer contains a ligand zone, within which there is a ligand. When the ligand zone is wet, the ligand can diffuse to bind the analyte via the analyte's ligand-binding site and subsequently form a detectable analyte-ligand complex. As set forth in claim 14, the

claimed invention requires that the analyte, which forms a detectable complex with the ligand, be "immobilized on a molecular analyte solid support."

In contrast, Greenquist describes a different multi-layer detection device for detecting the specific binding between an analyte-ligand pair. This device contains a minimal of two layers: a reagent layer containing an immobilized analyte, and a detection layer containing an immobilized detection reagent, which generates a detectable signal upon interacting with the label portion of a labeled ligand that specifically binds the analyte (see column 5, lines 54-66). In the alternative, the device may contain a third layer in addition to the above-mentioned two layers: an optional layer providing a labeled reagent (*i.e.*, a label moiety attached to a ligand that specifically binds the analyte) is placed next to the reagent layer, so that the reagent layer is sandwiched between this additional layer and the detection layer (see column 5, line 66, to column 6, line 3, and column 6, lines 18-25).

Using either one of these two designs by Greenquist, an analyte present in a liquid test sample first comes into contact with a labeled ligand, which may be supplied directly into the sample or by the optional layer. Also, as the Examiner has pointed out in the Advisory Action of October 17, 2006, a labeled ligand can be provided by way of pre-binding to the immobilized analyte in the reagent layer. Upon contact with a test solution, the binding between the labeled ligand and immobilized analyte becomes reversible and the labeled ligand can dissociate from the immobilized ligand and then bind to the free analyte from the test solution. In any one variation of the Greenquist device, a complex forms between a free analyte from the test solution and a labeled ligand. With the test solution, this analyte-(labeled ligand) complex can diffuse through the reagent layer into the detection layer and generate a detectable signal through the label moiety. On the other hand, any potential unbound labeled ligand is captured by the immobilized analyte in the reagent layer and therefore cannot diffuse into the detection layer to generate any false signal (see column 6, lines 26-57). Thus, the only detectable signal from a Greenquist device is generated from a complex between a free analyte from

a test solution and a labeled ligand, neither of which is immobilized at the moment the two bind and form a detectable complex. Indeed, both analyte and ligand have to migrate through at least the reagent layer to arrive at the detection layer in order to produce a detectable signal. While immobilized analyte is present in the reagent layer, such immobilized analyte serves only to sequester excessive, unbound labeled ligand and does not participate in the formation of a signal-generating complex. In other words, Greenquist does not provide the limitation of ***an analyte that is immobilized in one layer and specifically binds a ligand to produce a detectable product.***

3. The Anticipation Rejection Is Based on Flawed Reasoning

In the final Office Action of June 20, 2006, and again in the Advisory Action of October 17, 2006, the Examiner argues that the analyte and ligand are interchangeable concepts as binding partners (last paragraph on page 3 of the final Office Action), and that the term "molecular ligand" can encompass a complex between the analyte and ligand (first paragraph on page 4 of the Action). Appellant does not agree. First, the terms "analyte" and "ligand" in the pending claims are not merely equal binding partners, since they have features distinguishing one from the other. For instance, an "analyte" is immobilized to a fixed location whereas a "ligand" is capable of diffusing within a ligand zone upon wetting. These terms thus cannot simply switch places in the claims. Second, although the term "molecular ligand" is broadly defined in the specification, the context in which this term is used in the claims requires the interpretation that a "molecular ligand" is just a ligand alone without being in a complex with its binding partner "molecular analyte." Otherwise, the language in part (ii) of claim 14 "the molecular ligand can diffusibly migrate to the molecular ligand binding site of the molecular analyte to produce a detectable product" would make no sense at all. The Examiner's interpretation of a "molecular ligand" to mean a "complex of a molecular analyte and a molecular ligand" is simply illogical and unreasonable. More importantly, even if the Examiner's assertions were correct, the Greenquist reference would still fail to

provide at least one claim limitation: an analyte that is immobilized in the analyte layer and a component of a signal-generating complex of analyte-ligand.

In the Advisory Action mailed October 17, 2006, the Examiner maintains the anticipation rejection, stating that Greenquist does provide the limitation of an analyte that is immobilized in one layer and specifically binds a ligand to produce a detectable product, because the reference describes "a labeled reagent that is incorporated within the device, by being retained in the reagent zone and is free to migrate into the detection zone and capable of being bound to the immobilized interactive detection reagent in the detection zone" (the second paragraph on page 2 of the Advisory Action). The Examiner is apparently referring to one variation of the Greenquist device, where the labeled ligand is provided by way of prebinding to the immobilized analyte in the reagent layer. Because the binding between analyte and ligand is reversible in solution, when the device is in contact with a test solution containing free analyte, labeled ligand becomes dissociated with immobilized analyte and subsequently binds free analyte to form a complex. This complex then freely migrates into the detection layer to generate a detectable signal (column 10, lines 12-20, of Greenquist). As already discussed in the last section, regardless of how the labeled ligand is supplied, the labeled ligand as well as the analyte being tested (*i.e.*, the analyte from the test solution) are always mobile at the time the two form a detectable complex. The labeled ligand remains bound to the immobilized analyte in the reagent layer does not migrate into the detection layer to produce a detectable signal. The Greenquist device therefore does not teach an analyte that is immobilized in one layer and specifically binds a ligand to produce a detectable product.

The Examiner further argues in the Advisory Action that: (1) the reagent layer of Greenquist is equivalent to the film layer of this invention, because each contains an immobilized molecule; and (2) the detection layer of Greenquist is equivalent to the analyte layer of this invention, because each contains an immobilized analyte (the second paragraph on page 2 of the Advisory Action). Appellant again respectfully disagrees.

The Examiner is mistaken in point (1) because nothing in independent claim 14 of this application requires the film layer to contain an immobilized molecule. In fact, claim 14 recites, in the pertinent part, that "the film layer comprises a molecular ligand zone having a molecular ligand, wherein, upon wetting of the molecular ligand zone, the molecular ligand can diffusibly migrate to the molecular ligand binding site of the molecular analyte to produce a detectable product." Insofar as point (2) is concerned, the Examiner is incorrect to equate the detection layer of Greenquist and the analyte layer of this application, even though each indeed contains an immobilized analyte. This is because the Examiner has neglected to take into consideration that the immobilized analyte of this invention and Greenquist's immobilized analyte are used for directly opposite purposes. In the present invention, the immobilized analyte acts to form a detectable complex with a labeled ligand; whereas the role of Greenquist's immobilized analyte is to eliminate the potential false signal from excessive unbound labeled ligand. In short, the layers of Greenquist's device are not equivalent to the layers of the claimed device in this application.

As such, Appellant contends that the anticipation rejection lacks support by sound reasoning.

4. Summary

It has not been properly established that the Greenquist reference provides every limitation of the pending claims. The anticipation rejection is therefore improper and should be withdrawn.

B. The Rejection for Obviousness Is Improper

The Examiner has further rejected claims 23 and 24 under 35 U.S.C. §103(a), alleging that the claimed invention is obvious over Greenquist in view of the disclosure by Bergstrom (U.S. Patent No. 5,436,161). Appellant respectfully traverses the rejection and argues that the rejection is improper.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

As discussed above, Greenquist does not provide all limitations of independent claim 14, from which both claims 23 and 24 ultimately depend. On the other hand, the secondary reference by Bergstrom *et al.* was cited to supply the limitation of hydrogel, which is pertinent to claims 23 and 24 but not to claim 14. In other words, Bergstrom does not provide the missing limitations of claim 14 (which are missing limitations of claims 23 and 24 as well) that Greenquist has failed to provide. Thus, when considered together, the two cited references fail to provide all limitations of claims 23 and 24. As such, no *prima facie* obviousness has been established. The obviousness rejection under 35 U.S.C. §103(a) is therefore improper and should be withdrawn.

VIII. CONCLUSION

In view of the foregoing, Appellant believes that all claims now pending in this Application are in condition for allowance.

Respectfully submitted,

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IX. CLAIMS APPENDIX

14. An apparatus comprising a molecular analyte layer and a film layer wherein:

(i) the molecular analyte layer comprises a molecular analyte immobilized on a molecular analyte solid support, wherein said molecular analyte comprises a molecular ligand binding site; and

(ii) the film layer comprises a molecular ligand zone having a molecular ligand, wherein, upon wetting of the molecular ligand zone, the molecular ligand can diffusibly migrate to the molecular ligand binding site of the molecular analyte to produce a detectable product.

15. The apparatus of claim 14, wherein:

(i) said molecular analyte comprises a first component of a donor-acceptor pair;

(ii) said molecular ligand comprises a second component of said donor-acceptor pair; and

(iii) said detectable product is a complex between the molecular ligand and the molecular analyte, wherein the position of the first component of the donor-acceptor pair relative to the second component of the donor-acceptor pair allows detection of the complex.

16. The apparatus of claim 15, wherein said molecular analyte is a nucleic acid or a protein.

17. The apparatus of claim 15, wherein said molecular ligand is a nucleic acid or a protein.

18. The apparatus of claim 14, wherein:

(i) said molecular analyte comprises an enzyme;

(ii) said molecular ligand binding site is an active site of the enzyme;

(iii) said molecular ligand comprises an enzyme substrate; and

(iv) said detectable product is the enzyme substrate after being catalyzed by the enzyme.

19. The apparatus of claim 14, wherein said molecular analyte is immobilized on said molecular analyte solid support by binding said molecular analyte to a capture agent immobilized on said molecular analyte solid support, wherein said binding is a molecular analyte specific binding event.

20. The apparatus of claim 19, wherein said capture agent is a protein or nucleic acid.

21. The apparatus of claim 14, wherein said film layer is a multilayered film layer, wherein said multilayered film layer comprises the molecular ligand zone and at least one additional zone, wherein said additional zone comprises a chemical or physical environment that is distinguishable from the molecular ligand zone.

22. The apparatus of claim 21, wherein said additional zone is below said molecular ligand zone and is porous or water soluble.

23. The apparatus of claim 14, wherein said molecular ligand zone comprises a molecular ligand within a hydrogel.

24. The apparatus of claim 23, wherein said hydrogel comprises acrylamide or agarose.

25. The apparatus of claim 14, wherein said film layer comprises at least two molecular ligands, wherein said at least two molecular ligands are distributed in an array format.

X. EVIDENCE APPENDIX

Greenquist (U.S. Patent No. 4,806,312) and Bergstrom (U.S. Patent No. 5,436,161), made of record in Office Action mailed September 26, 2005.

XI. RELATED PROCEEDINGS APPENDIX

None.

X. EVIDENCE APPENDIX

1. Greenquist 4,806,312

X. EVIDENCE APPENDIX

2. Bergstrom *et al.* 5,436,161

Disclaimer

5,436,161—Jan Bergstrom, Balinge; Stefan Lofas, Uppsala; Bo Johnsson, Storvreta, all of Sweden. MATRIX COATING FOR SENSING SURFACES CAPABLE OF SELECTIVE BIOMOLECULAR INTERACTIONS, TO BE USED IN BIOSENSOR SYSTEMS. Patent dated July 25, 1995. Disclaimer filed Mar. 27, 1998, by the assignee, Biacore AB.

The term of this patent shall not extend beyond the expiration date of Pat. No. 5,242,828.

(Official Gazette, September 8, 1998)